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(54) Delivery system.

(57) A delivery system for agents, such as therapeutic agents, or other substances includes a biodegradable polymer and the agent or substance. The delivery system is coated with a barrier substance that decreases the quantity of the agent release from the system, compared to the quantity of the agent release from a system not coated with the substance, in the forty-eight hours period immediately subsequent to the parenteral injection or implantation of the system into a living person or annimal.

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Description

DELIVERY SYSTEM

This invention is concerned with release of agents, such as therapeutic agents, or other substances from delivery systems, and provides novel delivery systems, methods of administrating such agents or substances to vertebrates other than in therapy or in a method of diagnosis and methods of providing such delivery systems.

Biogradable polymers containing a therapeutic agent are often used to administer the agent to a patient. Generally the release results from the dissolution of the polymer and from the diffusion of the agent through pores and channels in the matrix.

According to a first aspect thereof, the invention provides a delivery system adapted for delivery of an agent, such as a therapeutic agent, or other substance to a living person or animal, comprising a biodegradable polymer and a therapeutic agent, characterised in that said delivery system, is coated with a barrier substance that is effective operatively to decrease the quantity of said agent or substance released from said system, compared with the quantity of said agent or substance released from a said system not coated with said substance, in a period of forty-eight hours immediately subsequent to parenteral injection or implantation of said system into a living person or animal.

In preferred embodiments, the barrier substance is silicone oil that has a viscosity of between 10^2 centipoise (cp) and 10^4 cp.

In a second and alternative aspect, the invention provides a method of providing a delivery system adapted for delivery of an agent, such as a therapeutic agent, or other substance to a living person or animal, characterised in comprising the steps of: coating a delivery system comprising a biodegradable polymer and said agent or substance with a barrier substance effective to decrease the quantity of said agent or substance released from said system, compared with the quantity of said agent or substance released from a said system not coated with said substance, in a period of forty-eight hours immediately subsequent to the parenteral injection or implantation of said system into a living person or animal; and treating said delivery system to remove some but not all of said barrier substance.

In some preferred embodiments, the barrier substance is a silicone oil, and the treating includes washing the delivery system with a solvent that removes some of the barrier substance.

Delivery systems consisting of a biodegradable polymer and a therapeutic agent are made in a variety of ways, e.g., solvent casting, coacervation procedures, or dispersion. When the former procedure is used, the agent is dispersed as small particles throughout the system. The small particles are irregularly shaped with small jagged edges; the edges may extend to the surface of the system, or may cause cracks in the system that extend to the surface. When such a system is inserted into a patient, a dose of agent larger than the desired dosage is released from the system through these surface contacts.

Delivery systems prepared by coacervation consist of an aggregate of agent surrounded by the polymer. The large crystal may have jagged edges extending to the surface, or may cause cracks that extend to the surface. Accordingly, the initial burst of agent problem is also present in these systems.

Coating the surface of the delivery system in either case with a barrier substance as taught herein limits the release of agent from the delivery system for the initial one or two day period following administration, thus decreasing the agent's possible deleterious side effects that can result from initial bursts of high agent release. In addition, because the initial quantity of agent release is limited, more agent remains in the system allowing for a longer effective period of use for the matrix.

The delivery system is easy to use and inexpensive to make. Moreover, because of the coating, the delivery system has superior handling properties in that it does not clump together when in powdered form.

The agent or substance concerned need not be for use in therapy or for diagnosis of desease in the recipient. The invention accordingly provides, in a third alternative aspect thereof, a method of administering an agent or substance to a vertebrate other than in therapy or in a method of diagnosis of disease by the use of a delivery system comprising a biodegradable polymer and said agent or substance; characterised in that it includes the steps of: coating said delivery systems with a barrier substance; and injecting or implanting the coated delivery system into said vertebrate, said barrier substance being effective to limit the initial release of said agent or substance from said system in comparison with the initial release obtained when a said system is not coated with said substance.

The invention is hereinafter more particularly described by way of example with reference to release of therapeutic agents.

The delivery system employs a biodegradable polymer containing a therapeutic agent. The system is coated with a barrier substance; the barrier substance, when the system is introduced into a vertebrate (preferably a mammal such as a human or domestic animal such as a dog or cow) decreases the initial burst of therapeutic agent from the system.

A biodegradable polymer is a polymer which slowly dissolves or degrades in a physiological environment into low molecular weight molecules that are then transported from the site. Types of biodegradable polymers suitable for use in a delivery system include polyanhydrides, partially crosslinked proteins, polylactic acid, polyglycolic acid, polyorthoesters, polysaccharides, polaxomers, hydroxypropylcellulose, polyethyleneglycol, copolymers of lactide and glycolide, and carboxymethylcellulose. Some representative examples of poly(lactide/glycolide) biodegradable polymers are described by Kitchell & Wise, 112 Methods in Enzymology 436

(1985).

The delivery systems produced in accordance with the teaching of the present invention preferably are injected or implanted parenterally into an animal or a human. Where the system is to be injected, it should be small enough in diameter to fit through the needle tip of the syringe. The preferred delivery systems for injection have an average size of 500 microns or less (more preferably 250 microns or less, most preferably 100 or 200 microns); rod shaped systems of 1-10 mm diameter, which generally are long and slender, may also be used.

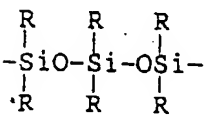
The term therapeutic agent, as used herein, means any agent used to treat or prevent any disease or disorder of the body. Representative agents include hormones (and hormone fragments and analogues), e.g., testosterone, luteinizing hormone-releasing hormone (LHRH); diuretics, e.g., chlorothiazide; anti-inflammatories; pain killers, e.g. morphine; antibiotics, e.g., tetracycline; antipsychotic drugs; anticancer drugs, e.g., methotrexate, actinomycin D, vinblastine, and cytosine arabinoside; vaccines; and antiarthritic drugs, e.g. ibuprofen, flurbiprofen.

Certain such agents, and others, may be administered to animals, such as animals grown for their milk, meat or skin products (e.g. wool or leather) other than for therapy or for diagnosing diseases in such animals.

One of the roles of the barrier substance is to limit the initial burst of agent from the delivery system. The barrier substance should not affect the long term sustained release of the agent, and therefore should be a substance that dissolves or wears off the surface of the system within a short period of time after injection; preferably, the barrier substance should dissipate within 5 days after injection, more preferably within 2 days after injection. The substance should be non-toxic, non-irritating, non-sensitizing, and hydrophobic. Preferably the substance is on the GRAS list or is USP approved.

Examples of suitable barrier substances include paraffins, beeswax, and, preferably, silicone oils.

Silicone oils are organo-siloxane polymers based on a structure consisting of alterating silicon and oxygen atoms with organic groups (R) attached to the silicon atoms:



Typical silicone oils include those in which R is a lower alkyl group having six or less carbons, e.g., a methyl group. Silicone oils have a viscosity of between 1 cp and 10^6cp. The more preferred silicone oils have a viscosity of between 10^2 cp and 10^4 cp; most preferably the silicone oils have a viscosity of between 500 cp and 2000 cp. Representative examples of silicone oils include Union Carbide dimethylpolysilicone #L-45 (viscosity 1000 cp), Dow Corning medical grade silicone oil #360, Aldrich silicone oil (catalogue no. 17,563-3). and Aldrich silicone oil (catalogue no. 14,615-3).

The delivery system can comprise up to 70% agent by weight. If a system comprises greater than 70% agent by weight, the mechanical properties of the system may be adversely affected.

The uncoated delivery system can be prepared by standard solvent casting techniques. In general, the polymer is dissolved in an organic solvent and the therapeutic agent added. The solution or suspension is then poured into a suitable mould and the solvent evaporated to yield a polymer-agent combination. Alternatively, the agent can be dispersed with the polymer without solvent.

The delivery system can also be prepared by coacervation procedures, such as those described by Lapka et al., U.S. Pat. No. 4,622, 244, the disclosure of which is hereby incorporated by reference.

The uncoated delivery system of choice (generally in the form of a powder) is placed in a flask and covered with a silicone oil such as Union Carbide dimethylpolysilicone #L-45. The thickness of the coating can be adjusted by rinsing with hexane or other organic solvent capable of dissolving silicone oil. The thicker the coating, the more limited the initial burst of release of agent from the system. The powder is dried under a stream of nitrogen gas, and then under vacuum for 24 hours.

Alternate methods of coating including spraying a thin coat of silicone oil onto the powder; and mixing the powder in a solvent in which the barrier substance has been dissolved and then evaporating off the solvent.

Where the delivery system is a powder made up of particles having an average size 100-200 microns, following coating each particle should be 0.05%-10% (more preferably 0.1%-2%) silicone oil by weight. The amount of silicone oil present can be calculated by first conducting an elemental analysis of the powder to determine the amount of silicon present; knowing the percentage of silicon in the oil, the amount of oil can then be determined.

The delivery systems containing the standard dosage of the selected therapeutic agent and coated with a barrier substance are injected, implanted, or otherwise inserted parenterally into a patient. The barrier substance limits the initial burst of the agent from the polymer; over a short period of time, the barrier substance wears off of the surface of the system, allowing the system to release the desired dosage over a sustained period of time.

A comparison of the initial quantity of agent released from the coated delivery system and an uncoated delivery system can be made by (1) injecting or implanting equal amounts (uncoated weight) of the systems into different animals; and (2) either determining the levels of agent in the animal's blood after 48 hours, or measuring the biological effect that the agent induces (e.g., for delivery systems that release LHRH, the level of testosterone in serum is measured, that level being directly correlated to the amount of LHRH released). It is understood that, although it is most preferred that the initial release be limited to the desired dosage of

the agent, advantages, such as reducing side effects of large dosages of the agent, are achieved if the initial release is reduced by as little as ten percent (more preferably twenty percent).

Claims

1. A delivery system adapted for delivery of an agent, such as a therapeutic agent, or other substance to a living person or animal, comprising a biodegradable polymer and a therapeutic agent, characterised in that said delivery system, is coated with a barrier substance that is effective operatively to decrease the quantity of said agent or substance released from said system, compared with the quantity of said agent or substance released from a said system not coated with said substance, in a period of forty-eight hours immediately subsequent to parenteral injection or implantation of said system into a living person or animal.

2. A delivery system according to Claim 1, further characterised in that said barrier substance is a silicone oil.

3. A delivery system according to Claim 2, further characterised in that said silicone oil has a viscosity of between 10^2 centipoise and 10^4 centipoise.

4. A delivery system according to Claim 3, further characterised in that said silicone oil has a viscosity of between 500 centipoise and 2000 centipoise.

5. A method of administering an agent or substance to a vertebrate other than in therapy or in a method of diagnosis of disease by the use of a delivery system comprising a biodegradable polymer and said agent or substance; characterised in that it includes the steps of: coating said delivery system with a barrier substance; and injecting or implanting the coated delivery system into said vertebrate, said barrier substance being effective to limit the initial release of said agent or substance from said system in comparison with the initial release obtained when a said system is not coated with said substance.

6. A method according to Claim 5, further characterised in that said barrier substance is a silicone oil.

7. A method according to Claim 6, further characterised in that said silicone oil has a viscosity of between 10^2 centipoise and 10^4 centipoise.

8. A method according to Claim 7, further characterised in that said silicone oil has a viscosity of between 500 centipoise and 2000 centipoise.

9. A method of providing a delivery system adapted for delivery of an agent, such as a therapeutic agent, or other substance to a living person or animal, characterised in comprising the steps of: coating a delivery system comprising a biodegradable polymer and said agent or substance with a barrier substance effective to decrease the quantity of said agent or substance released from said system, compared with the quantity of said agent or substance released from a said system not coated with said substance, in a period of forty-eight hours immediately subsequent to the parenteral injection or implantation of said system into a living person or animal; and treating said delivery system to remove some but not all of said barrier substance.

10. A method according to Claim 10, further characterised in that said barrier substance is a silicone oil.

11. A method according to Claims 9 or 10, further characterised in that said treating comprises washing said delivery system with a solvent.

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EUROPEAN SEARCH REPORT

Application Number

EP 88 30 6958

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
P,A	EP-A-0 263 083 (R. VALDUCCI et al.) * claims * ---	1-11	A 61 K 9/30 A 61 K 9/22
Y	US-A-4 351 337 (K.R. SIDMAN et al.) * claims * ---	1-11	
Y	WO-A-8 704 070 (RESEARCH CORPORATION) * page 3, lines 3-9; claims * ---	1-11	
A	EP-A-0 206 890 (A.E.C. - SOCIETE DE CHIMIE ORGANIQUE ET BIOLOGIQUE) * page 3, lines 24-29; claims * ---	1-11	
A	US-A-3 854 480 (A. ZAFFARONI et al.) * column 3, line 58 - column 4, line 27; claims * ---	1-11	
A	DE-A-2 824 112 (GARCHING INSTRUMENTE) * claims * ---	1-11	
A,D	US-A-4 622 244 (G.G. LAPKA et al.) * claims * -----	1-11	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	02-04-1990	SIATOU E

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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Agricultural cultivating and sowing combination.

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Equivalents: ☐ DE3738134

Cited Documents: DE8707011U; DE3105641; FR2499817; US4088083; US4509438; FR2586336

Abstract

Agricultural cultivating and sowing combination, consisting of a soil-cultivating appliance (1), of a follow-up roller (2) which is arranged behind the soil-cultivating appliance and which is so connected via supporting arms (5) to the leading soil-cultivating appliance that the latter can move freely upwards to a certain extent in relation to the follow-up roller, and of a removable semi-mounted seed drill (3), the dispensing member of which is driven by an element (21, 38) rolling on the ground, the seed drill being semi-mountable on differently designed soil-cultivating appliances with different follow-up rollers. To improve considerably the known cultivating and sowing combination, the seed drill can be semi-mounted directly on the follow-up rollers, the seed drill can be coupled by means of coupling elements (16) to the follow-up roller or its supporting arms or supporting frame, and the seed drill can be semi-mounted directly on differently designed follow-up rollers, depending on the design of the follow-up roller the dispensing member of the seed drill being driven by the follow-up roller or by an additional wheel rolling on the ground or by another power source preferably adjustable or controllable by means of an electronic path-dependent control.